Real-world experience of SGLT2 inhibitors: A useful addition to the arsenal of antidiabetes medication. An Irish perspective

Patricia Harkin, Ann Fitzpatrick, Ber Lynch, Siobhan Hatton, Ronan Canavan, Malachi McKenna, Donal O'Shea

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Article points

1. This real-world Irish audit was conducted to assess the effects of sodium–glucose cotransporter 2 inhibitor treatment in 30 people with type 2 diabetes in terms of weight and HbA_{1c}.
2. Mean HbA_{1c} reduced by 13 mmol/mol (1.2%) and mean weight by 2.9 kg over the course of the audit.
3. Genital mycotic infections occurred in 20% of participants but did not result in discontinuation of the medication.

Key words

- Real-world study
- SGLT2 inhibitors
- Type 2 diabetes

Authors

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Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been approved for use in the Republic of Ireland since 2014. In clinical trials, this class of agent has been shown to reduce HbA_{1c} by up to 11 mmol/mol (1.0%), as well as reducing weight by an average of 2 kg, compared with placebo. The aim of this audit was to evaluate the effects and safety profile of SGLT2 inhibitors in a real-world cohort of people with type 2 diabetes treated at three hospitals in St Vincent's Healthcare Group in Dublin. Thirty people with up to 15 months' exposure to SGLT2 inhibitor therapy were evaluated. The results revealed an acceptable efficacy and safety profile, suggesting that these agents are a useful contribution to diabetes care in the clinical setting.

Since 2009, the medical management of people with type 2 diabetes has changed dramatically with the introduction of dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors. This article focuses on the SGLT2 inhibitor class and presents an Irish audit highlighting positive benefits in terms of weight and HbA_{1c} in a group of people with type 2 diabetes who were seen in outpatient clinics.

SGLT2 inhibitors

There are three SGLT2 inhibitors licensed in the Republic of Ireland. Dapagliflozin (Forxiga; AstraZeneca) 5 mg and 10 mg was the first to market in April 2014. This was followed by empagliflozin (Jardiance; Boehringer Ingelheim) 10 mg and 25 mg in November 2014. Canagliflozin (Invokana; Janssen-Cilag) 100 mg and 300 mg was last to market in Ireland, in January 2015, but was first to market in the US, and it now has 3 years of post-marketing data available. All of these agents are also now available in fixed-dose combinations with metformin, under the names Xigduo (with dapagliflozin), Synjardy (with empagliflozin) and Vokanamet (with canagliflozin).

Inzucchi et al (2015) highlighted key points in relation to SGLT2 inhibitors in an update to a joint position statement of the American Diabetes Association (ADA) and European Association for the Study of Diabetes. In clinical trials, the agents reduced HbA_{1c} by up to 11 mmol/mol (1.0%). They act by inhibiting SGLT2 in the proximal nephron, reducing glucose reabsorption and increasing glucose excretion by up to 80 g/day. The rate of glucose excretion is even higher with canagliflozin, at 77–119 g/day, equivalent to a loss of 308–476 kcal/day (Seufert, 2015). Additional effects of SGLT2 inhibitors include weight loss of approximately 2 kg, lowering of systolic blood pressure by 2–4 mmHg and diastolic blood pressure by 1–2 mmHg, and reductions in plasma uric acid levels and albuminuria (Inzucchi et al, 2015). Owing to their mechanism of action, SGLT2 inhibitors are less effective when the estimated glomerular filtration rate (eGFR) is <45–60 mL/min/1.73 m^2.

The first research demonstrating positive cardiovascular outcomes with an SGLT2 inhibitor

was published in 2015. In the EMPA-REG OUTCOME study, treatment with empagliflozin resulted in a 38% reduction in the risk of cardiovascular mortality and a 32% reduction in all-cause mortality compared with placebo in people with type 2 diabetes at high cardiovascular risk (Zinman et al, 2015). There was also a 39% reduction in the risk of incident or worsening nephropathy (Wanner et al, 2016). Initial reductions in eGFR with empagliflozin, possibly due to hyperfiltration, stabilised after 4 weeks.

The manufacturers of the other SGLT2 inhibitors are currently conducting cardiovascular safety studies to determine whether these renal and cardiac benefits are a class effect. The results of CANVAS (Canagliflozin Cardiovascular Assessment Study) and DECLARE (Dapagliflozin Effect on Cardiovascular Events) are expected in 2017 and 2019, respectively.

Concerns and safety issues

Side effects of SGLT2 inhibitors include genital mycotic infections, which occur in around 11% of women and 4% of men (Nyirjesy et al, 2014). The agents have a diuretic effect and small, reversible increases in serum creatinine levels occur (Inzucchi et al, 2015). There can also be small increases in LDL cholesterol levels.

Increased urinary calcium excretion has been observed with canagliflozin treatment, and the US Food and Drug Administration has mandated the follow-up of upper limb fractures with this agent (Inzucchi et al, 2015).

Euglycaemic diabetic ketoacidosis (DKA) has emerged as a potential complication with SGLT2 inhibitors (Peters et al, 2015). However, the majority of cases were seen in people with type 1 diabetes, in whom SGLT2 inhibitors are not licensed for use. There were two cases in people with type 2 diabetes, both of whom had recently undergone surgery – one 12 hours previously, the other within the previous week.

As a result of the concerns about DKA, a direct healthcare professional communication (DHPC) was issued by the Irish Health Products Regulatory Authority (HPRA, 2015). Healthcare professionals were advised that people who presented with acidosis were to be tested for ketones and that patients should be informed of the symptoms of metabolic acidosis and advised to seek medical assistance in the event of nausea, vomiting, anorexia, pain, thirst, breathing difficulties, confusion, unusual fatigue or sleepiness. Suspected adverse reactions were to be reported to the HPRA.

A further DHPC update was issued on 21 March 2016 as the outcome of an evaluation (HPRA, 2016). It stated that atypical, rare but serious, sometimes life-threatening DKA could occur even 2 months after commencing SGLT2 inhibitor therapy. Healthcare professionals were again cautioned to inform patients of symptoms of metabolic acidosis. If this is suspected or diagnosed, the medication should be discontinued and not restarted unless a cause is determined. Treatment should be interrupted in hospitalised patients, those with acute illness and those undergoing surgery. Caution should be exercised when treating people with a history of alcohol abuse or pancreatitis.

We discussed the concerns about DKA at our weekly multidisciplinary team journal club, and the negativity seen in these publications contradicted our clinical experiences with SGLT2 inhibitors. As a result, this audit was initiated. The findings were first presented in poster format at the clinic audit masterclass study day at St Vincent's University Hospital.

Dublin audit

This audit was carried out between July and September 2015. In our institutions, the ADA (2016) treatment algorithm for antihyperglycaemic therapy in people with type 2 diabetes (*Figure 1*) is followed. This recommends SGLT2 inhibitors as an option in dual or triple therapy to achieve HbA_{1c} targets. Consequently, a total of 94 people were receiving SGLT2 inhibitors at the time of the audit. This class of medication is relatively new to Ireland, and this audit generally saw them initiated as a second- to sixth-line agent for the management of glycaemic control. Metformin was ruled out as a treatment option in a number of people owing to intolerance.

Participant characteristics

All participants had type 2 diabetes. Thirty-three were being treated at St Vincent's Private Hospital; of these, 28 were prescribed dapagliflozin and five empagliflozin. Thirty-three were

Page points

1. Empagliflozin was the first sodium–glucose cotransporter 2 (SGLT2) inhibitor to demonstrate a cardioprotective effect in clinical trials, and other studies are underway to determine whether this is a class effect.
2. Chief safety concerns with SGLT2 inhibitors are an increased risk of genitourinary infections and a rare but serious side effect of euglycaemic ketoacidosis.
3. The current audit comprised 94 outpatients with type 2 diabetes receiving SGLT2 inhibitor therapy, of whom 30 had follow-up data available.

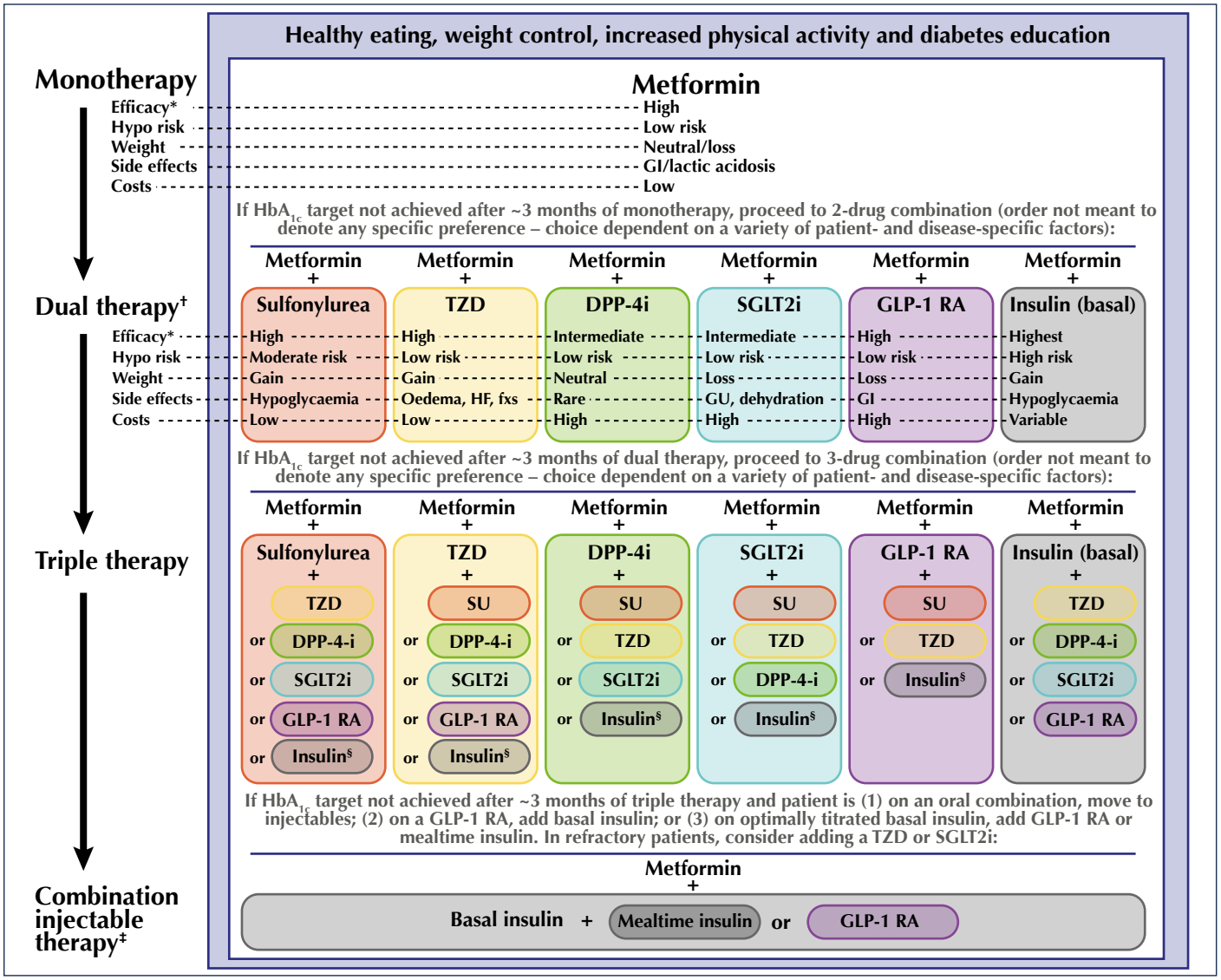

Figure 1. Algorithm used in St Vincent's Healthcare Group, Dublin. Reproduced from American Diabetes Association (2016).
The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycaemic therapy for people with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances).
DPP-4i=dipeptidyl peptidase-4 inhibitor; fxs=fractures; GI=gastrointestinal; GLP-1 RA=glucagon-like peptide-1 receptor agonist; GU=genitourinary; HF=heart failure; hypo=hypoglycaemia; SGLT2i=sodium–glucose cotransporter 2 inhibitor; SU=sulfonylurea; TZD=thiazolidinedione.
**See Inzucchi et al (2015) for description of efficacy categorisation. †Consider starting at this stage when HbA_{1c} is ≥75 mmol/mol (9%). ‡Consider starting at this stage when blood glucose is ≥16.7–19.4 mmol/L and/or HbA_{1c} is ≥86–108 mmol/mol (10–12%), especially if symptomatic or catabolic features are present, in which case basal insulin plus mealtime insulin is the preferred initial regimen. §Usually a basal insulin (NPH, glargine, detemir, degludec).*

treated at St Michael's Hospital, of whom 20 received dapagliflozin, 10 empagliflozin and three canagliflozin. Twenty-eight were treated at St Vincent's University Hospital, of whom 18 received dapagliflozin, seven empagliflozin and three canagliflozin.

Of the 94 participants, 30 had returned to clinic for review since initiation of SGLT2 inhibitors and are reviewed in this article. Their demographics and treatment outcomes are summarised in *Table 1*.

Discussion

SGLT2 inhibitors were well tolerated in this cohort of people with type 2 diabetes in the outpatient setting. Over treatment periods ranging from 2 to 15 months, HbA_{1c} increased in two people and remained

Table 1. Summary of audit findings in 30 people treated with sodium–glucose contransporter 2 inhibitors at three hospitals in Dublin.

	St Vincent's Private Hospital	St Michael's Hospital	St Vincent's University Hospital
n	11	13	6
Gender	1 female 10 male	6 female 7 male	2 female 4 male
Diabetes duration (mean [range]; years)	11.7 (1.5–20)	13.0 (5–24)	12.1 (4–16)
Age (mean [range]; years)	64.7 (43–77)	67.2 (42–77)	65.7 (44–89)
Baseline* BMI (mean [range]; kg/m^2)	31.6 (26.5–39.5)	29.5 (23.8–37.3)	31.9 (28.7–35.8)
SGLT2i treatment duration (mean [range]; months)	5.1 (2–6)	8.4 (3–14)	7.2 (3–15)
Weight loss (mean [range]; kg)	3.0 (0.9–6.2)	3.6 (–4.0† to 6.7)	2.1 (–0.4† to 4.4)
Baseline* HbA_{1c} (mean [range]; mmol/mol)	76 (60–105)	73 (60–98)	75 (68–81)
Baseline* HbA_{1c} (mean [range]; %)	9.1 (7.6–11.8)	8.8 (7.6–11.1)	9.0 (8.4–9.6)
HbA_{1c} reduction (mean [range]; mmol/mol)	16 (3–35)	12 (–11† to 28)	10 (–13† to 23)
HbA_{1c} reduction (mean [range]; %)	1.5 (0.3–3.2)	1.1 (–1.0‡ to 2.6)	0.9 (–1.2‡ to 2.1)
Genitourinary infections (*n*)	3	2	1

*Baseline defined as initiation of SGLT2i therapy. †Three people had increases in weight ranging from 0.4 to 4.0 kg. ‡HbA_{1c} increased in two people.
SGLT2i=sodium–glucose cotransporter 2 inhibitor.

unchanged in another; all other participants had reductions in HbA_{1c} ranging from 3 to 35 mmol/mol (0.3–3.2%). The average reduction in HbA_{1c} was 13 mmol/mol (1.2%). This is clinically significant given that the UKPDS (UK Prospective Diabetes Study) showed that, for every 11 mmol/mol (1.0%) reduction in HbA_{1c}, there were 21% reductions in the relative risk (RR) of diabetes-related endpoints and of diabetes-related death, a 14% reduction in the RR of myocardial infarction and a 37% reduction in the RR of microvascular complications (Stratton et al, 2000).

Three people had increases in weight of 0.4–4.0 kg and all others had reductions ranging from 0.1 to 6.7 kg. The average weight loss was 2.9 kg. Genital mycotic infections occurred in six participants (20%) but did not result in discontinuation of the medication. We witnessed a good safety profile with these medications in our small sample size.

A number of the participants had their best glycaemic control in years or ever, and some were able to achieve their target HbA_{1c} levels for the first time. For some, the weight loss was also the best achieved in years or on record. No significant changes in lipid levels, albumin:creatinine ratio or

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1. Over a treatment period ranging from 2 to 15 months, mean HbA_{1c} fell by 13 mmol/mol (1.2%) following initiation of SGLT2 inhibitor therapy, and mean body weight fell by 2.9 kg.
2. Genital mycotic infections occurred in 20% of participants but did not lead to treatment discontinuation. No other safety concerns were observed.

Authors

Patricia Harkin is Advanced Nurse Practitioner/Registered Nurse Prescriber, St Vincent's Private Hospital, and Adjunct Lecturer, University College Dublin; Ann Fitzpatrick is Diabetes Nurse Specialist/ Registered Nurse Prescriber, St Michael's Hospital; Ber Lynch is Clinical Nurse Manager, Diabetes, St Michael's Hospital; Siobhan Hatton is Diabetes Nurse Specialist, St Vincent's University Hospital; Ronan Canavan is Consultant Endocrinologist, St Vincent's University Hospital, St Vincent's Private Hospital and St Columcille's Hospitals; Malachi McKenna is Consultant Endocrinologist, St Vincent's Healthcare Group; Donal O'Shea is Consultant Endocrinologist, St Vincent's University Hospital, St Vincent's Private Hospital and St Columcille's Hospitals, Dublin.

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serum creatinine levels were noted. Improvements in blood pressure were noted in some participants. However, it was not possible to rule out an element of white coat hypertension (elevated blood pressure owing to anxiety about the medical environment) in some people.

We currently do not use SGLT2 inhibitors in the inpatient setting, as these people are more vulnerable and volume depletion could also be an issue. However, we will continue to monitor the efficacy of this drug class in the outpatient setting.

Conclusion

In this real-world audit of 30 people with type 2 diabetes, treatment with SGLT2 inhibitors resulted in clinically significant reductions in HbA_{1c} and body weight. The safety profile was good. Side effects typically associated with this class of medication were common but did not lead to treatment discontinuation in any participant. ■

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